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Paclitaxel-coated balloons versus percutaneous transluminal angioplasty for infrapopliteal chronic total occlusions: the IN.PACT BTK randomised trial

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KEYWORDS

- below-the-knee disease
- chronic limb-threatening ischaemia
- drug-coated balloon
- total occlusion

Abstract

Background: Data are mixed concerning the safety and effectiveness of drug-coated balloons (DCBs) for treating below-the-knee (BTK) lesions.

Aims: The aim of this study was to assess the safety and effectiveness of the IN.PACT 014 paclitaxel-coated balloon catheter versus conventional percutaneous transluminal angioplasty (PTA) for infrapopliteal chronic total occlusions (CTOs) in patients with chronic limb-threatening ischaemia (CLTI).

Methods: The IN.PACT BTK randomised study is a prospective, multicentre, randomised pilot study. Fifty CLTI participants (Rutherford clinical category 4-5) with BTK CTOs were randomised 1:1 to DCB (N=23) or PTA (N=27). The primary effectiveness endpoint was late lumen loss (LLL) at 9 months post procedure. Safety outcomes up to 9 months included all-cause mortality, major target limb amputation, and clinically driven target lesion revascularisation (CD-TLR).

Results: Mean lesion length was 215.41±83.81 mm in the DCB group and 218.19±80.43 mm for PTA (p=0.806). The 9-month angiographic LLL was 0.892±0.774 mm for the DCB group and 1.312±0.720 mm for the PTA group (p=0.070) in a classic analysis, and 0.592±0.944 mm for DCB and 1.260±0.810 mm for PTA (p=0.017) in a subsegmental analysis. The Kaplan-Meier estimated freedom from CD-TLR up to 9 months was 91.1% for DCB and 91.8% for PTA (log-rank p=0.942). At 9 months, 1 patient died in the DCB group and 2 in the PTA group (p=1.000); there were no major target limb amputations in either arm.

Conclusions: The 9-month subsegmental LLL was lower after treatment with the IN.PACT 014 DCB compared with PTA with no differences in safety or revascularisation events in a small complex population of patients with BTK CTOs. ClinicalTrials.gov: NCT02963649

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Abbreviations

BTK	below-the-knee
CD-TLR	clinically driven target lesion revascularisation
CLTI	chronic limb-threatening ischaemia
CTO	chronic total occlusion
DCB	drug-coated balloon
DUS	duplex ultrasound
LLL	late lumen loss
MAE	major adverse event(s)
MLD	minimal lumen diameter
PTA	percutaneous transluminal angioplasty
RCC	Rutherford clinical category
TLR	target lesion revascularisation

Introduction

Chronic limb-threatening ischaemia (CLTI) is an advanced form of peripheral artery disease with significant below-the-knee (BTK) involvement[1]. Revascularisation is the guideline-recommended treatment for patients with CLTI[2]; however, chronic total occlusions (CTOs) are highly prevalent among patients with CLTI and remain a challenging variant for treatment. Although bypass surgery is an important option for the treatment of BTK lesions, endovascular interventions have been on the rise, as many patients suffer from underlying comorbidities that result in high surgical risk. Conventional percutaneous transluminal angioplasty (PTA) has been the primary endovascular intervention used for the infrapopliteal vascular bed, despite the poor long-term patency rates (42-75% at one year) associated with this procedure[3].

Paclitaxel drug-coated balloons (DCBs) have been compared to conventional PTA for the treatment of BTK lesions, though studies resulted in mixed outcomes[4-10]. Inconsistent findings across studies suggest a need for further investigation and an evaluation of opportunities for enhanced rigour in study design. Furthermore, there are no DCB studies that specifically reported outcomes for patients with infrapopliteal CTOs.

The IN.PACT 014 paclitaxel-coated balloon catheter (IN.PACT 014 DCB; Medtronic) is part of the IN.PACT family of paclitaxel DCBs. While similar in design to the IN.PACT Admiral DCB (Medtronic), which is approved for the treatment of femoropopliteal lesions, the IN.PACT 014 DCB is an investigational product compatible with a 0.014" guidewire for BTK vessels. The IN.PACT BTK randomised study was designed to assess the safety and effectiveness of the IN.PACT 014 DCB versus PTA for the treatment of CLTI patients with CTOs in the infrapopliteal arteries.

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Methods

STUDY DESIGN

The IN.PACT BTK randomised study is a prospective, multicentre, randomised study to evaluate the safety and effectiveness of the IN.PACT 014 DCB for the treatment of infrapopliteal CTOs in CLTI patients (Rutherford clinical category [RCC] 4-5), as previously described[11] (**Supplementary Appendix 1**). Participants who met all inclusion/exclusion criteria including successful predilation of the target lesion(s) were enrolled from March 2017 to February 2019, across nine study sites **(Supplementary Table 1)** and randomised 1:1 into DCB (N=23) or PTA (N=27) treatment groups. Participants were followed up to 30 days, 3, 6, and 9 months, and will continue to be followed up to 12, 24 and 36 months, though the sponsor intends to extend the follow-up of the study up to 60 months. Angiographic assessments were performed at the nine-month visit or sooner in case of a target lesion revascularisation (TLR). Participants with ischaemic wounds on the target limb at baseline, or who developed a new ischaemic wound on the target limb during the study, had an additional overlapping follow-up schedule (once per week for the first month, and then once a month until healed) at a dedicated wound care facility or with a wound care specialist. Participant flow through the study is shown in **Figure 1**.

An independent data safety monitoring board monitored the study and an independent clinical events committee (Syntactx, Herzele, Belgium) adjudicated all major adverse events (MAE) including revascularisation events. An independent duplex ultrasound (DUS) core laboratory (VasCore, Boston, MA, USA) and an angiography core laboratory (Cardiovascular Imaging Core Laboratory, Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA, USA) analysed all images. The clinical events committee and core laboratories were blinded to treatment.

The study is being conducted in accordance with the Declaration of Helsinki, and federal, national and local laws, regulations, standards, and requirements of the countries where the study is being conducted. The study protocol was reviewed and approved by the ethics committees and/or competent authorities, and all participants provided written informed consent prior to enrolment. The study is registered at ClinicalTrials.gov (NCT02963649).

INDEX PROCEDURE

Participants were administered dual antiplatelet therapy per institutional standard of care. Inflow vessels with flow-limiting lesions were treated before the index procedure, with successful treatment defined by a ≤30% residual diameter stenosis. All eligible participants underwent a predilation of the target lesion with a non-drug-coated semi-compliant balloon. According to the core laboratory DUS guidelines for measuring reference vessel diameter, the predilation balloon was sized at a 1:1 ratio to the vessel wall, and a length that covered the entire length of the target lesion. More than one predilation balloon was allowed, and the balloon could be inflated more than once according to protocol. No other vessel preparation devices, such as cutting/scoring balloons, were permitted. Angiography and DUS were used to determine predilation success, which was defined as angiographic residual stenosis ≤30% per visual estimate, and intraprocedural Doppler exam showing a biphasic (with rapid take-off) or triphasic wave signal, with absence of a major (grade D or greater) flow-limiting dissection (observed on two orthogonal views).

For the PTA group, no additional treatment was performed after enrolment and randomisation. Participants randomised to the DCB

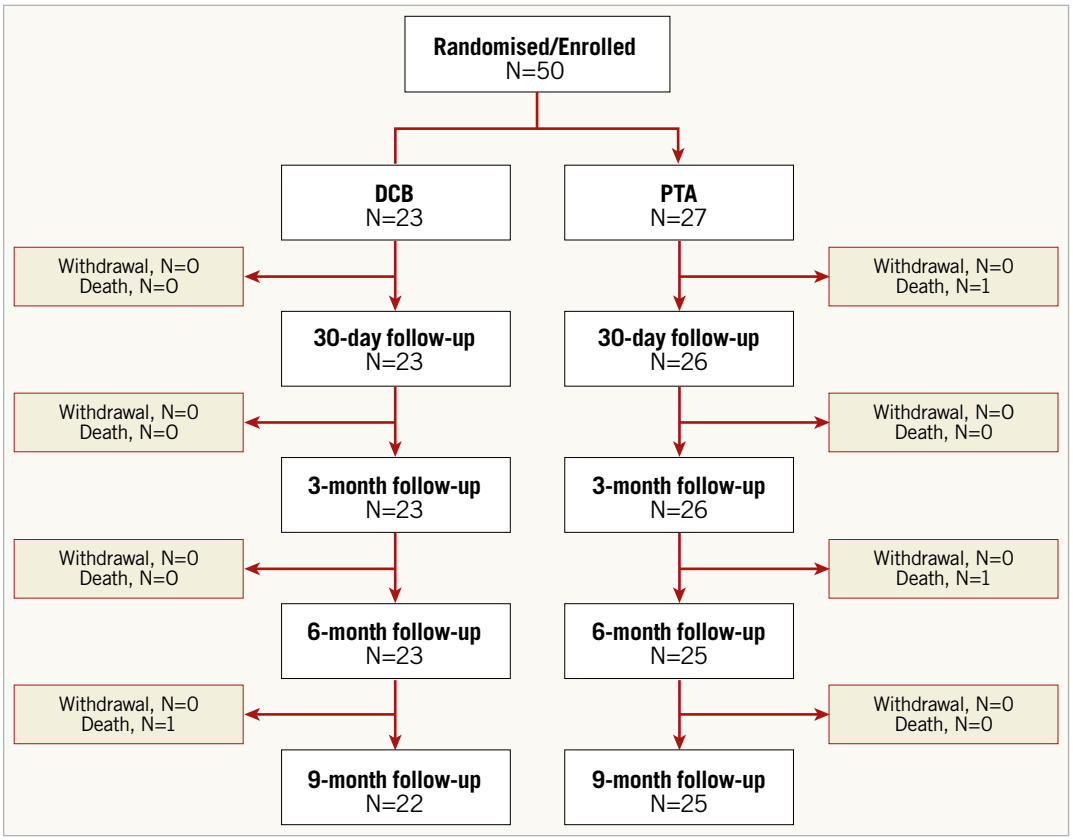


Figure 1. *CONSORT flow diagram up to nine months in the IN.PACT BTK randomised study. Participant numbers reported at each time point are eligible participants. DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty*

group received the IN.PACT 014 DCB. Details of the IN.PACT 014 catheter device have been described previously[11]. If a participant had multiple target lesions, all lesions were treated with the same assigned randomised treatment. Prolonged balloon inflation was allowed to manage a suboptimal result, including >50% residual stenosis, perforation, occlusive complication, or flow-limiting dissection. Bail-out stenting was allowed if prolonged balloon inflation did not provide the expected result. Other adjunctive therapies were not allowed. This included laser, atherectomy, cryoplasty, cutting/scoring balloons, and brachytherapy.

ENDPOINTS AND ASSESSMENTS

The primary effectiveness endpoint was late lumen loss (LLL) at nine months post procedure for DCB versus PTA as measured by the classic and subsegmental angiographic analyses. LLL was defined as the difference between the minimal lumen diameter (MLD) immediately post procedure and MLD at nine-month angiographic follow-up (or at the time of TLR) and assessed using classic and subsegmental angiographic techniques. The classic angiographic method for measuring LLL was suggested to be inadequate in long and diffused lesions (Razavi M. Transverse View Area Loss [TVAL]: An informative angiographic outcome in BTK lesions. The Leipzig Interventional Course [LINC]. 2020, January 28-31, Leipzig, Germany). A subsegmented angiographic method for measurement of LLL was described previously[11], and was shown to be suitable for angiographic efficacy evaluation[12]. Briefly, in this method, each treated length was divided into a tandem array of ten equally spaced subsegments. Subsegmental measures were taken to determine the mean and minimal diameters within each subsegment, which were matched with the baseline, post-procedural, and follow-up angiograms. These values were compiled into a data series and used to generate an overall mean value for the target lesion. Angiographic outcomes obtained by subsegmental analysis at nine months post procedure included subsegmental LLL, subsegmental acute luminal gain (defined as the difference between subsegmental MLD immediately post procedure and subsegmental MLD at baseline), loss index with subsegmental MLD (defined as LLL divided by acute luminal gain), number of subsegments with ≥50% stenosis per lesion, and number of occluded subsegments (100% stenosis) per lesion at nine months post procedure. Other angiographic outcomes assessed included acute luminal gain, loss index with MLD, diameter stenosis, and binary restenosis (≥50%) at nine months post procedure.

Secondary endpoints included: a composite safety endpoint within nine months (composite of freedom from device- and procedure-related mortality within 30 days, freedom from major target limb amputation and freedom from clinically driven TLR [CD-TLR] within nine months post procedure), MAE rate up to

nine months (composite of all-cause mortality, major target limb amputation, and CD-TLR), mechanically driven TLR (defined as any TLR due to a flow-limiting dissection or flow-limiting thrombosis at the target lesion that occurs within 37 days post procedure documented by a DUS peak systolic velocity ratio >2.4 and confirmed by angiography), and any TLR, any target vessel revascularisation (TVR), clinically driven target vessel revascularisation (CD-TVR), and thrombosis at the target lesion(s) within nine months. CD-TLR is defined as any TLR of the target lesion with restenosis >70% (confirmed by angiography) associated with at least one of the following: reoccurrence of ischaemic rest pain, worsening of pre-existing wounds or occurrence of new wound(s). Clinical improvement at nine months was assessed with an evaluation of RCC and functional flow (defined as the absence of target lesion occlusion [no flow] on DUS).

STATISTICAL ANALYSIS

This is a pilot study including a new DCB platform, the IN.PACT 0.14, the performance of which in terms of safety and efficacy was unknown. Pilot studies do not have the statistical power of large trials but may provide scientific signals to be validated in larger studies. The number of patients considered valuable for this type of investigation is between 30 and 50[13]. Analyses were based on the intent-to-treat principle. Baseline demographics and characteristics are summarised on a patient basis, and lesion characteristics on a lesion basis. Continuous variables are described as mean±standard deviation, and comparisons between groups were performed with the t-test or Wilcoxon rank-sum test in case normality was violated. Dichotomous and categorical variables are described as proportions and counts, and comparisons between groups were performed with Fisher's exact test. The Kaplan-Meier method was used to evaluate time-to-event data for freedom from CD-TLR, freedom from the composite safety endpoint, freedom from MAE, and freedom from all-cause mortality over the nine-month follow-up period. The log-rank test was used for comparison between groups. For event rates that are expressed as a proportion, the number of participants with an event within 270 days was the numerator and the total number of participants with an event or at least 210 days of clinical follow-up was the denominator. Overall missing data were not imputed, and the level of statistical significance was set at 0.05 for a two-sided test. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results

PARTICIPANT AND LESION CHARACTERISTICS

Baseline demographic, clinical, and lesion characteristics were similar between the groups **(Table 1)**. The mean age was 73.1±7.4 years in the DCB group and 69.6±9.4 years in the PTA group (p=0.107). Both groups had a high incidence of diabetes mellitus (DCB 73.9% and PTA 96.3%; p=0.039). The mean lesion length was 215.4±83.8 mm in the DCB group and 218.2±80.4 mm in the PTA group (p=0.806). Approximately half of the lesions in each group were calcified (DCB 54.2%, PTA 41.4%; p=0.410), with 8.3% of DCB lesions and 13.8% of PTA lesions having severe calcification.

PROCEDURAL CHARACTERISTICS

Most lesions in the PTA group (73.3%) had three or more predilations compared with 48.0% in the DCB group (p=0.087) **(Supplementary Table 2)**. The rate of provisional stenting was 8.0% in the DCB group and 3.3% for PTA (p=0.586). While the occurrence of periprocedural dissections was not significantly different between the groups (p=0.108), there was a trend towards more ≥grade B dissections in the DCB group (54.2%) versus PTA (27.6%) **(Supplementary Table 2)**. Acute angiographic outcomes were similar between the groups. Immediately post procedure, MLD was 1.945±0.412 mm in the DCB group and 1.797±0.462 mm for PTA (p=0.230), and diameter stenosis was 31.843±10.959% for DCB and 34.124±14.368% for PTA (p=0.703). Final residual stenosis was 5.1±7.6% for DCB and 6.8±8.5% for PTA (p=0.432) **(Supplementary Table 2)**.

ANGIOGRAPHIC EFFECTIVENESS OUTCOMES

There was a trend of lower LLL at nine months in the DCB group (0.892±-0.774 mm) compared to PTA (1.312±0.720 mm; p=0.070) in the classic analysis, which was statistically significant in the subsegment analysis (0.592±0.944 mm for DCB vs 1.260±0.810 mm; p=0.017) **(Table 2)**. The mean loss index was 0.534±0.482 for DCB and 0.755±0.332 for PTA (p=0.116), and the rates of binary restenosis (≥50%) were 70.0% for DCB and 83.3% for PTA in the classic analysis (p=0.472) **(Table 2)**. The subsegmental loss index was significantly lower for DCB versus PTA (0.486±0.726 versus 0.786±0.417; p=0.030). The number of subsegments with ≥50% residual stenosis was lower in the DCB group (mean 2.800±3.286) compared with the PTA group (5.250±3.721; p=0.036). The number of occluded subsegments (100% stenosis) was 1.900±3.227 in the DCB group versus 3.292±3.557 in the PTA group (p=0.150). The individual subsegmental MLD values measured at baseline (pre-procedure), immediately post procedure, and at nine months post procedure are reported for each group in the **Central illustration**.

SECONDARY EFFECTIVENESS OUTCOMES

The Kaplan-Meier estimated freedom from CD-TLR up to nine months was 91.1% for DCB and 91.8% for PTA (log-rank p=0.942) **(Figure 2)**. Duplex ultrasound assessments showed that functional flow was persistent in the DCB group up to nine months. In the DCB group, 84.6% of lesions retained functional flow at nine months compared with 60.0% in the PTA group (p=0.341) **(Supplementary Table 3)**.

FUNCTIONAL OUTCOMES

The differences in RCC between baseline and nine months indicated clinical improvement in both groups **(Supplementary Figure 1)**. At baseline, all participants in each group were in RCC 4-5. At nine

Table 1. Baseline demographic, clinical and lesion characteristics from the IN.PACT BTK randomised study.

		DCB (N=23 participants) (N=25 lesions*)	PTA (N=27 participants) (N=30 lesions*)	*p*-value
Age, years		73.1±7.4 (23)	69.6±9.4 (27)	0.107
Male		82.6 (19/23)	74.1 (20/27)	0.515
Obesity, BMI ≥30 kg/m^2		22.7 (5/22)	26.9 (7/26)	1.000
Diabetes mellitus		73.9 (17/23)	96.3 (26/27)	0.039
Insulin-dependent		39.1 (9/23)	74.1 (20/27)	0.021
Hypertension		82.6 (19/23)	77.8 (21/27)	0.736
Hyperlipidaemia		72.7 (16/22)	80.0 (20/25)	0.732
Current smoker		17.4 (4/23)	11.5 (3/26)	0.692
End-stage renal disease◊		0.0 (0/23)	0.0 (0/27)	>0.999
Cerebrovascular disease		26.1 (6/23)	11.5 (3/26)	0.273
Congestive heart failure		8.7 (2/23)	19.2 (5/26)	0.424
Ischaemic heart disease		43.5 (10/23)	34.6 (9/26)	0.569
Bilateral PAD		54.5 (12/22)	63.6 (14/22)	0.760
Previous peripheral revascularisation of target limb		30.4 (7/23)	33.3 (9/27)	1.000
Previous minor target limb amputation		13.0 (3/23)	40.7 (11/27)	0.056
Rutherford clinical category	4	13.0 (3/23)	11.1 (3/27)	1.000
	5	87.0 (20/23)	88.9 (24/27)	
	6	0.0 (0/23)	0.0 (0/27)	
Target lesion location‡	Popliteal P3 segment	8.3 (2/24)	3.4 (1/29)	0.584
	Tibio-peroneal trunk	16.7 (4/24)	13.8 (4/29)	1.000
	Anterior tibial	70.8 (17/24)	51.7 (15/29)	0.174
	Posterior tibial	25.0 (6/24)	41.4 (12/29)	0.254
	Peroneal	4.2 (1/24)	6.9 (2/29)	1.000
Inflow in the target vessel (<30% residual stenosis)‡,§		90.0 (18/20)	87.5 (21/24)	1.000
Lesion type¶	De novo	80.0 (20/25)	86.7 (26/30)	0.717
	Restenotic (non-stented)	20.0 (5/25)	13.3 (4/30)	
Lesion length, mm‡		215.41±83.81 (24)	218.19±80.43 (28)	0.806
Occluded¶,#		100.0 (25/25)	100.0 (30/30)	>0.999
Total occluded lesion length, mm‡		159.00±84.66 (21)	136.43±72.82 (22)	0.353
Diameter stenosis, %‡		97.59±6.69 (24)	96.33±8.64 (29)	0.473
Reference vessel diameter, mm‡		2.80±0.54 (24)	2.71±0.39 (29)	0.835
Minimum lumen diameter, mm‡		0.06±0.19 (24)	0.09±0.21 (29)	0.511
Calcification‡,**		54.2 (13/24)	41.4 (12/29)	0.410
Mild/moderate		12.5 (3/24)	13.8 (4/29)	
Moderate/severe		33.3 (8/24)	13.8 (4/29)	
Severe		8.3 (2/24)	13.8 (4/29)	
TASC II‡	A	4.2 (1/24)	0.0 (0/29)	0.504
	B	4.2 (1/24)	13.8 (4/29)	
	C	66.7 (16/24)	58.6 (17/29)	
	D	25.0 (6/24)	27.6 (8/29)	

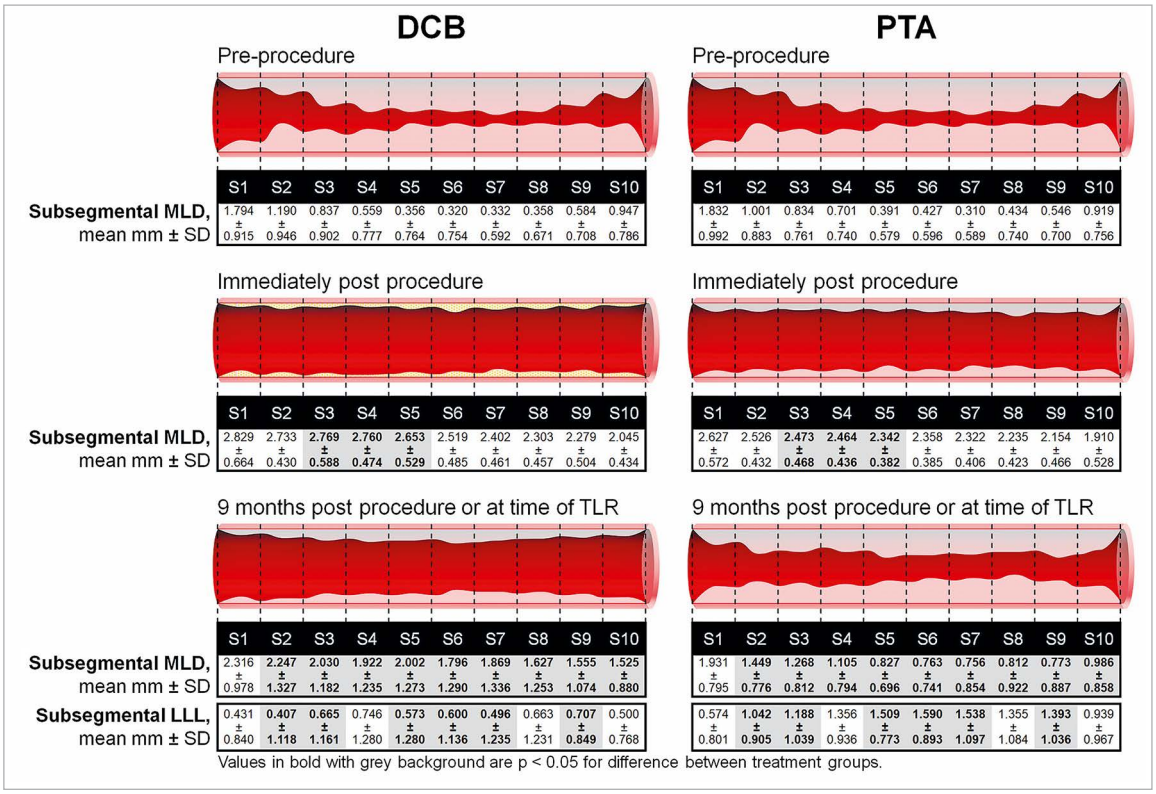
Values are mean±SD (N) or % (n/N). * The study sites and core laboratory identified different numbers of target lesions in each treatment group. Study sites identified 25 target lesions in the DCB group and 30 in the PTA group. Therefore, all site-reported lesion characteristics use 25 as the denominator for the DCB group and 30 as the denominator for the PTA group. The core laboratory identified 24 target lesions in the DCB group and 29 in the PTA group. Therefore, all core laboratory-reported lesion characteristics use 24 as the denominator for the DCB group and 29 as the denominator for the PTA group. ◊ Participants with impaired renal function (glomerular filtration rate <20 mL/min) and/or on dialysis were not enrolled in the study. ‡ Core laboratory reported. § Participant-based assessment. ¶ Site reported. # Participants must have had a site-assessed chronic total occlusion to be enrolled in the study. ** Calcification was scored by the angiographic core laboratory (Cardiovascular Imaging Core Laboratory, Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA, USA). Mild to moderate calcification was defined as calcium visible along one side of the arterial wall in the area of the target lesion prior to injection of contrast. The calcium present encompasses <50% of the total target lesion treatment area by visual estimate and/or calcium is not circumferential (360°) in nature (i.e., on both sides of the vessel lumen extending 2 cm or greater on a single AP view) or classified as exophytic calcification and does not impede blood flow in the vessel. Moderate to severe calcification was defined as calcium visible along one or both sides of the arterial wall in the area of the target lesion. The calcium present encompasses ≤50% of total target lesion treatment area by visual estimate and/or the calcium is not circumferential (360°) in nature (i.e., on both sides of the vessel lumen extending 2 cm or greater on a single AP view) or classified as exophytic calcification and does not impede blood flow by more than 50%. Severe calcification was defined as calcium visible along both sides of the arterial wall, covering 2 cm or greater of the target lesion area, encompassing greater than 50% of the total target lesion treatment area by visual estimate and/or calcium is circumferential (360°) in nature (i.e., on both sides of the vessel lumen extending 2 cm or greater on a single AP view) or classified as exophytic calcification, significantly impeding blood flow in the vessel. BMI: body mass index; DCB: drug-coated balloon; PAD: peripheral artery disease; PTA: percutaneous transluminal angioplasty; TASC: Trans-Atlantic Inter-Society Consensus

Table 2. Angiographic outcomes up to nine months from the IN.PACT BTK randomised study.

	DCB (N=24 lesions*)	PTA (N=29 lesions*)	Difference [95% CI]	*p*-value
Classic analysis				
LLL, mm◊	0.892±0.774 (20)	1.312±0.720 (24)	–0.420 [–0.875, 0.035]	0.070
MLD, mm	0.949±0.835 (20)	0.498±0.597 (24)	0.451 [0.014, 0.887]	0.056
Acute lumen gain, mm‡	1.881±0.431 (24)	1.707±0.518 (29)	0.174 [–0.092, 0.441]	0.367
Loss index§	0.534±0.482 (20)	0.755±0.332 (24)	–0.222 [–0.470, 0.027]	0.116
Diameter stenosis, %	67.827±27.984 (20)	80.547±22.920 (24)	–12.720 [–28.201, 2.761]	0.130
Binary restenosis (≥50%), %	70.0 (14/20)	83.3 (20/24)	–13.3% [–37.4%, 11.3%]	0.472
Subsegmental analysis				
LLL, mm◊	0.592±0.944 (19)	1.260±0.810 (24)	–0.668 [–1.209, –0.128]	0.017
Acute lumen gain, mm‡	1.838±0.738 (23)	1.602±0.575 (29)	0.236 [–0.130, 0.602]	0.201
Loss index§	0.486±0.726 (19)	0.786±0.417 (24)	–0.300 [–0.683, 0.084]	0.030
Number of subsegments with ≥50% stenosis	2.800±3.286 (20)	5.250±3.721 (24)	–2.450 [–4.608, –0.292]	0.036
Number of occluded subsegments (100% stenosis)	1.900±3.227 (20)	3.292±3.557 (24)	–1.392 [–3.476, 0.693]	0.150

Values are mean±SD (N) or % (n/N). *Core laboratory analysis determined a total of 24 target lesions in the DCB group and 29 target lesions in the PTA group. All core laboratory-based assessments use these values for counts and proportions. ◊Late lumen loss is defined as the difference between MLD at 9 months post procedure and MLD immediately post procedure. ‡Acute lumen gain is defined as the difference between MLD immediately post procedure and MLD at baseline. § Loss index is defined as LLL divided by acute lumen gain. CI: confidence interval; DCB: drug-coated balloon; LLL: late lumen loss; MLD: minimal lumen diameter; PTA: percutaneous transluminal angioplasty

months, only 15.0% of the DCB group and 8.7% of the PTA group were still in RCC 4–5. The majority of participants in each group were RCC 0-2 (DCB 75.0% and PTA 82.6%), and more than half in each group were RCC 0 (DCB 55.0% and PTA 60.9%). The RCC distribution was not significantly different between groups at nine months (p=0.895).



Central illustration. *Subsegmental array angiographic analysis from pre-procedure up to nine months in the IN.PACT BTK randomised study. Individual subsegmental MLD values were measured pre-procedure, immediately post procedure, and at nine months post index procedure. Corresponding nine-month subsegmental LLL values are also shown. P-values are for differences in matching subsegmental LLL between groups at nine months post procedure. DCB: drug-coated balloon; LLL: late lumen loss; MLD: minimal lumen diameter; PTA: percutaneous transluminal angioplasty; SD: standard deviation; TLR: target lesion revascularisation*

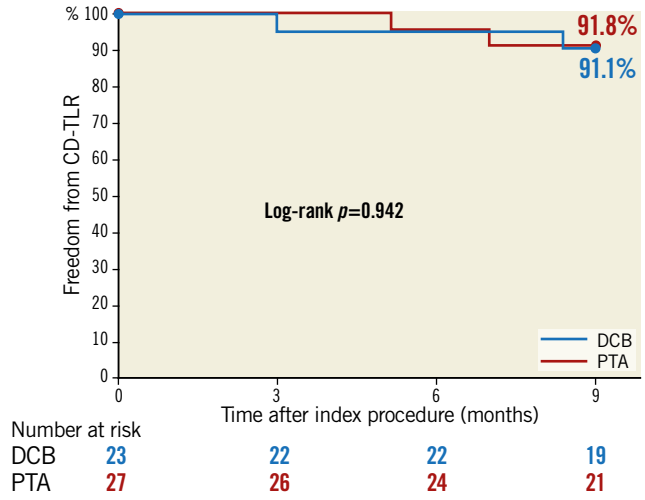


Figure 2. *Kaplan-Meier estimates of freedom from CD-TLR up to nine months in the IN.PACT BTK randomised study. CD-TLR: clinically driven target lesion revascularisation; DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty*

SAFETY OUTCOMES UP TO NINE MONTHS

There were no differences between groups in safety events within nine months **(Table 3 and Figure 3)**. The composite safety endpoint was achieved by 91.3% of participants in the DCB group and 87.5% in the PTA group (p=1.000). The rate of MAE was 13.0% in the DCB group and 16.0% for PTA (p=1.000). One death occurred in the DCB group at 232 days post procedure and two in the PTA group, at 17 days post procedure and at 162 days post procedure, all of which were cardiovascular-related deaths (DCB: respiratory failure at 232 days; PTA: myocardial infarction at 17 days, recurrent pulmonary embolism at 162 days). As adjudicated by the clinical events committee, none of these deaths were device- or paclitaxel-related. The Kaplan-Meier estimated nine-month freedom from all-cause death rates are shown in **Figure 3**. There were no major target limb amputations in either group and the rate of thrombosis at the target lesion(s) was comparable between groups (DCB 4.3%, PTA 4.2%, p=1.000).

POST HOC SAFETY OUTCOMES UP TO 12 MONTHS

There were three deaths in the PTA arm and one death in the DCB arm, and no major target limb amputations in either arm up to 12 months.

Discussion

The IN.PACT BTK randomised study is a prospective, multicentre, feasibility pilot study evaluating the safety and effectiveness of the IN.PACT 014 DCB versus PTA for the treatment of patients with BTK CTOs. DCB angioplasty was effective in reducing LLL up to nine months compared to PTA, with similar safety outcomes between the groups. There were no major target limb amputations, and mortality rates were low up to 12 months in this complex patient population.

The mean lesion length in this study was over 21 cm in both groups, similar to what is expected in a real-world population with

Table 3. Safety outcomes up to nine months from the IN.PACT BTK randomised study.

	DCB (N=23 participants)	PTA (N=27 participants)	*p*-value
Composite safety endpoint*	91.3 (21/23)	87.5 (21/24)	1.000
Device- and procedure-related death within 30 days	0.0 (0/23)	3.7 (1/27)	1.000
Major target limb amputation within 9 months	0.0 (0/23)	0.0 (0/23)	>0.999
CD-TLR within 9 months◊	8.7 (2/23)	8.7 (2/23)	1.000
Major adverse events up to 9 months‡	13.0 (3/23)	16.0 (4/25)	1.000
Death, all-cause	4.3 (1/23)	8.0 (2/25)	1.000
Death, cardiovascular-related	4.3 (1/23)	8.0 (2/25)	1.000
Major target limb amputation	0.0 (0/23)	0.0 (0/23)	>0.999
CD-TLR	8.7 (2/23)	8.7 (2/23)	1.000
Mechanically driven TLR within 37 days§	4.3 (1/23)	0.0 (0/26)	0.469
Any TLR	8.7 (2/23)	16.7 (4/24)	0.666
CD-TVR¶	8.7 (2/23)	13.0 (3/23)	1.000
Any TVR	8.7 (2/23)	20.8 (5/24)	0.416
Thrombosis at the target lesion(s)	4.3 (1/23)	4.2 (1/24)	1.000

Values are % (n/N). *The composite safety endpoint is a composite of freedom from device- and procedure-related mortality within 30 days, and freedom from major target limb amputation and freedom from CD-TLR within 9 months after the index procedure. ◊CD-TLR is defined as any TLR of the target lesion with restenosis >70% (confirmed by angiography) associated with at least one of the following: reoccurrence of ischaemic rest pain, worsening of pre-existing wounds, or occurrence of a new wound(s). ‡Major adverse events defined as a composite of all-cause mortality, major target limb amputation, and CD-TLR. §Mechanically driven TLR is defined as any TLR due to a flow-limiting dissection or flow-limiting thrombosis at the target lesion that occurs within 37 days post procedure documented by a peak systolic velocity ratio >2.4. ¶CD-TVR is defined as any TVR of the target vessel associated with at least one of the following: reoccurrence of ischaemic rest pain, worsening of pre-existing wounds, or occurrence of a new wound(s). CD-TLR: clinically driven target lesion revascularisation; CD-TVR: clinically driven target vessel revascularisation; DCB: drug-coated balloon; PTA; percutaneous transluminal angioplasty; TLR: target lesion revascularisation; TVR: target vessel revascularisation

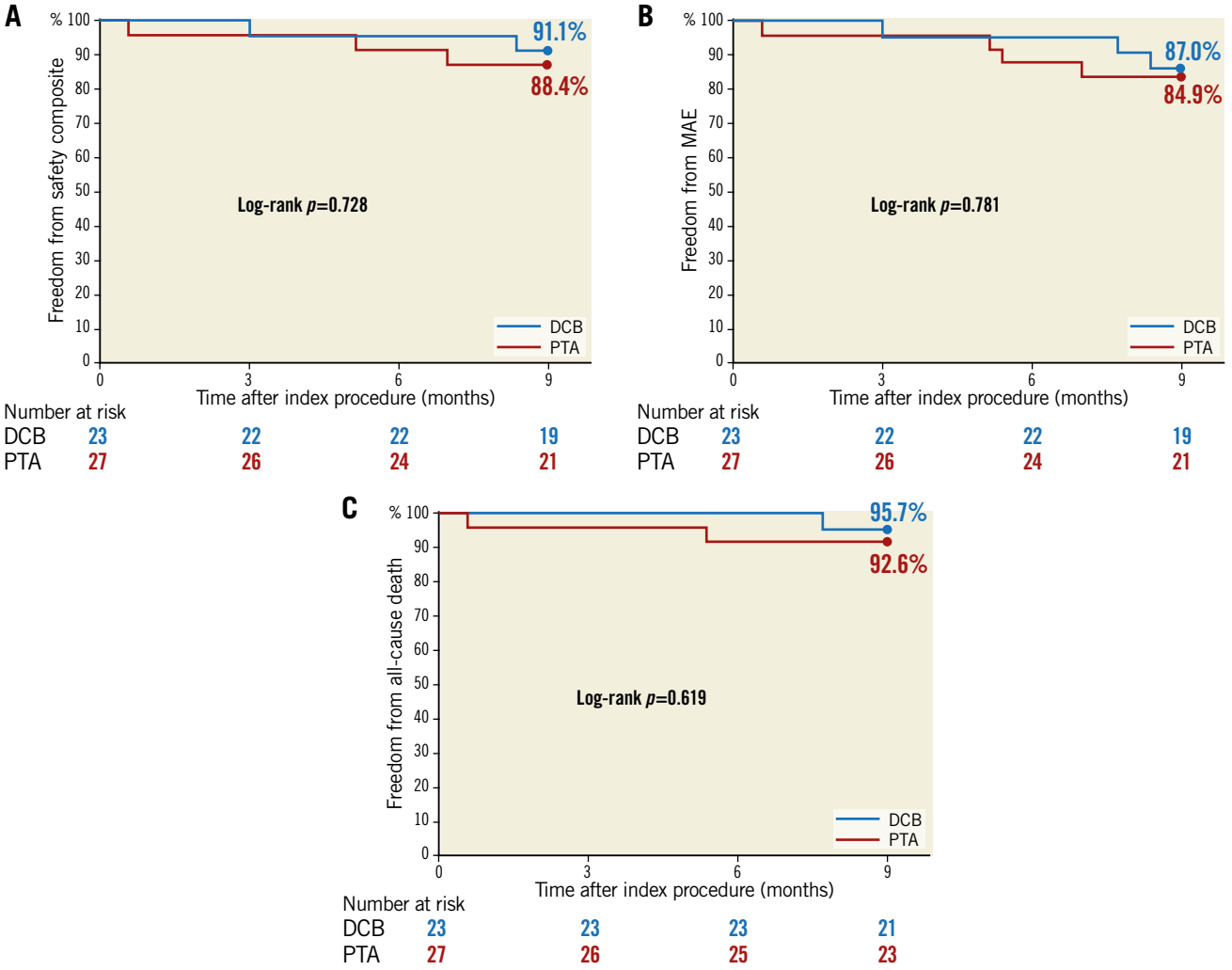


Figure 3. *Kaplan-Meier estimates of freedom from composite safety endpoint (A), freedom from MAE (B), and freedom from all-cause death (C) up to nine months in the IN.PACT BTK randomised study. DCB: drug-coated balloon; MAE: major adverse events; PTA: percutaneous transluminal angioplasty*

CLTI and diabetes. While direct comparisons are not possible, previous randomised controlled trials of BTK DCBs included simpler lesions with shorter lengths (<15 cm)[5-8,14] and often fewer CTOs (<40%)[6,14,15]. The IN.PACT BTK study design limited randomisation to lesions with successful predilation. This aspect of the study was meant to reduce disparities between study groups and make the comparison more reliable within a small sample size. Patients with suboptimal balloon angioplasty, whether due to significant residual stenosis or flow-limiting dissection, were not enrolled in the study. To ensure an optimal PTA, the predilation balloon was sized at a 1:1 ratio to the reference vessel diameter.

To better evaluate the efficacy of angioplasty in this complex lesion setting, the subsegment method of angiographic assessment for BTK treatment efficacy was previously introduced[11]. In this subsegmental method, a tandem array was employed to allow better assessment of MLD across the entire lesion as opposed to a single MLD measurement through the classic angiographic analysis. This method was especially helpful in the present study, considering the population of complex long lesions (mean lesion length of over 21 cm), in which the classic angiographic method of assessing LLL is considered inadequate (Razavi M. Transverse View Area Loss [TVAL]: An informative angiographic outcome in below-knee lesions. The Leipzig Interventional Course [LINC]. 2020, January 28-31, Leipzig, Germany). Although there was a reduction of >30% LLL with DCB compared to PTA at nine months in the classic analysis, the difference between groups was not significant, most likely due to the small sample size and the inadequate assessment method. When a subsegmental angiographic evaluation was used to assess LLL, there was a tenfold increase in the number of compared vessel segments that improved the power of analysis. As a result, the difference between DCB and PTA became larger with a relative reduction of >50% in favour of DCB, which was significant. The subsegmental analysis also revealed target lesion details that were otherwise unappreciated with classic analysis: the pattern of restenosis was focal after DCB treatment versus diffuse after PTA, and the number of target lesion subsegments that

had restenosis (>50%) in the DCB group was about half that of the PTA group at nine months. This difference may reflect a better distal perfusion irrespective of the absolute maximal LLL and minimal percentage diameter stenosis.

Due to the lesion length and exclusive enrolment of CTOs in this study, it is difficult to compare our results with those of previous trials. In the IN.PACT DEEP study, a trial that evaluated a different DCB (IN.PACT Amphirion; Medtronic), 12-month LLL was approximately 0.6 mm in each study arm among participants who were selected for angiographic evaluation[8]. In the IN.PACT DEEP angiography cohort, the mean lesion length was restricted to <10 cm and <40% of participants in each group had CTOs at baseline[8], which is unusual in patients with CLTI who often have long tibial occlusions[16]. In addition, 12-month angiography was performed in approximately 50% of the scheduled participants, which is low and weakens the validity of those results[8]. The primary outcomes of ACOART BTK performed with the Litos DCB (Acotec Scientific Holdings Ltd.) were recently published[10]. The outcomes between IN.PACT BTK and ACOART BTK are also not directly comparable since there are inherent trial design differences. For example, the primary endpoint was LLL at six months in ACOART BTK as opposed to nine months in IN.PACT BTK. Furthermore, lesion characteristics were more complex in IN.PACT BTK (lesion length, 21.5 cm in the DCB group, 21.8 cm in the PTA group; CTOs, 100% in both groups) compared to ACOART BTK (lesion length: 16.8 cm DCB, 18.7 cm PTA; CTOs: 67.7% DCB, 66.7% PTA). Nonetheless, the nine-month LLL of 0.59 mm (subsegmental analysis) or 0.89 mm (classic analysis) in the DCB arm of IN.PACT BTK was in line with that from ACOART BTK (6-month LLL was 0.51 mm for DCB). LLL in the PTA arms was also comparable in these two BTK trials (1.31 mm at 9 months in IN.PACT BTK and 1.31 at 6 months in ACOART BTK).

The IN.PACT BTK study was not powered to detect a difference in clinical endpoints, such as CD-TLR or other parameters. Recently, a meta-analysis of eight randomised trials, investigating BTK angioplasty with paclitaxel-coated balloons versus PTA, reported significantly worse 12-month amputation-free survival for paclitaxel-coated balloons[17]. However, there were no differences in the composite safety endpoint at 9 months or all-cause mortality at 12 months, both of which were numerically (but not statistically) better in the DCB group versus PTA. No major target limb amputations were reported in either treatment group up to 12 months. While this excellent finding is encouraging, we acknowledge that this study enrolled only patients with optimal balloon angioplasty and distal run-off to the foot, which excluded patients with high risk of early re-occlusion and insufficient foot perfusion, both risk factors for major amputation.

Strengths of this study include an improved balloon platform and a pre-specified wound management guide, which was absent in the IN.PACT DEEP trial. The investigational IN.PACT 014 DCB shares the same paclitaxel drug formulation of 3.5 µg/mm^2 in urea excipient as that of the IN.PACT Admiral DCB used in the IN.PACT SFA and IN.PACT Global trials, and approved for femoropopliteal lesions. The investigational IN.PACT 014 DCB is markedly different than the IN.PACT Amphirion DCB that was used in the IN.PACT DEEP BTK trial[8], including changes in balloon material and coating methods. The present study includes a pre-specified foot lesion healing programme with continuous monitoring of the healing process and patency by scheduled visits. This aspect is crucial for prompt diagnosis of lesion worsening and vessel re-occlusion and allows a fast track strategy for reintervention before the foot lesion becomes irreversible.

Study limitations

While the subsegmental method improved the power of analysis, the sample size was small to be statistically powered for events such as reinterventions. Due to the nature of the procedure, it was not possible to blind the operator or study site staff. In addition, participants were not blinded due to inherent differences in procedure between the DCB and PTA groups, for example procedure times, as the DCB group was treated with an additional balloon. While there was a strict schedule for wound care follow-up, wound information was collected by visual estimation only. Furthermore, granular wound care and offloading information for individual patients is not available.

Conclusions

At nine months, participants in the DCB group experienced a large separation (53% lower) in subsegmental LLL compared to those in the PTA group. Similarly, using the classic method, participants in the DCB group showed a trend of lower LLL compared to those in the PTA group. Safety outcomes were similar between the two arms. Future larger studies, utilising improved study design and analytical methods such as those described in this study, are warranted to confirm the safety and effectiveness of DCBs in CLTI patients with infrapopliteal lesions.

Impact on daily practice

Clinical studies, including randomised controlled trials, have shown mixed results on the safety and effectiveness of DCBs for the treatment of BTK lesions in patients with CLTI; study designs have come into question. The pilot IN.PACT BTK randomised study demonstrates that DCB angioplasty is feasible in CLTI patients with infrapopliteal chronic total occlusions, and suggests that the approach is safe with a potential added benefit over PTA by reducing late lumen loss as evaluated by classic angiographic and new subsegmental methods. The improved design of the IN.PACT BTK randomised study embraces inclusion criteria that reduce confounding factors, a new angiographic method that provides detailed subsegment information, a pre-specified wound care programme, and an improved DCB platform.

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Conflict of interest statement

F. Liistro is an advisory board member for Biotronik, Boston Scientific, Medtronic, and Philips. I. Weinberg is a consultant for Magneto Thrombectomy Solutions, a National Principal Investigator for Penumbra, Inc., and Medical Director of VASCORE, the Vascular Imaging Core Laboratory. A. Almonacid Popma receives no personal fees; her spouse, J. Popma, joined Medtronic as an employee after completion of the analysis but prior to publication. M.H. Shishehbor reports consultant income from Abbott Vascular, Boston Scientific, Medtronic, Philips, and Terumo. S. Deckers is a full-time employee of Medtronic. A. Micari is an advisory board member for Boston Scientific and Medtronic.

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Supplementary data

Supplementary Appendix 1. CONSORT 2010 checklist of information to include when reporting a randomised trial.

Supplementary Table 1. IN.PACT BTK randomised study sites and investigators.

Supplementary Table 2. Procedural characteristics and outcomes from the IN.PACT BTK randomised study.

Supplementary Table 3. Functional flow assessment by duplex ultrasound up to 9 months from the IN.PACT BTK randomised study.

Supplementary Figure 1. Rutherford clinical category at baseline and month 9 in the IN.PACT BTK randomised study.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00444

Supplementary data

Supplementary Appendix 1.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Yes
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Yes
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	Not included
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	P. 6 and published study design article (Micari, et al. *J Crit Limb Ischemia*. 2021)
	4b	Settings and locations where the data were collected	Suppl Table 1, p. 2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8 and published study design article
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	Published study design article
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not included
Randomisation:			

Sequence generation	8a	Method used to generate the random allocation sequence	Not included
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Published study design article
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Not included
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Published study design article
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	16-17
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	P. 6, Figure 1, Tables 1 and 2
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Not included
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Table 2 and Table 3
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Pp. 11-13, Tables 2 and 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA, all pre-specified
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	None reported
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Not included

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17-18
Other information			
Registration	23	Registration number and name of trial registry	Abstract (p. 2)
Protocol	24	Where the full trial protocol can be accessed, if available	Not included
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Supplementary Table 1. IN.PACT BTK randomised study sites and investigators.

Study site	Location	Investigators
Universitair Ziekenhuis Gent	Gent, Belgium	Frank Vermassen, MD, PhD
UniversitätsSpital Zürich	Zurich, Switzerland	Martin Banyai, MD Frederic Baumann, MD Robert Kreuzpointer, MD
Ziekenhuis Oost Limburg – Campus Sint-Jan	Genk, Belgium	Wouter Lansink, MD
Hôpital Guillaume et René Laënnec – CHU de Nantes	Nantes, France	Yann Gouëffic, MD, PhD Philippe Chaillou, MD
IRCCS Multimedica	Sesto San Giovanni, Italy	Flavio Airoldi, MD
University General Hospital of Patras	Patras, Greece	Konstantinos Katsanos, MD, PhD
AZ Sint-Blasius – Campus Dendermonde	Dendermonde, Belgium	Koen Deloose, MD
Maria Cecilia Hospital	Cotignola, Italy	Antonio Micari, MD, PhD Paolo Sbarzaglia, MD
Ospedale San Donato	Arezzo, Italy	Francesco Liistro, MD

Supplementary Table 2. Procedural characteristics and outcomes from the IN.PACT BTK randomised study.

	DCB (N=23 participants) (N=25 lesions*)	PTA (N=27 participants) (N=30 lesions*)	*p*-value
Inflow lesion treatment during index procedure†,§	43.5 (10/23)	51.9 (14/27)	0.584
Predilation†	100.0 (25/25)	100.0 (30/30)	>0.999
Number of predilations per lesion†			0.087
1	16.0 (4/25)	6.7 (2/30)	
2	36.0 (9/25)	20.0 (6/30)	
3	32.0 (8/25)	26.7 (8/30)	
>3	16.0 (4/25)	46.7 (14/30)	
Maximum predilation pressure per lesion, atm†	12.3±2.9 (25)	13.2±2.5 (30)	0.295
Number of DCB balloons per participant†			–
1	0.0 (0/23)	NA	
2	26.1 (6/23)	NA	
3	56.5 (13/23)	NA	
>3	17.4 (4/23)	NA	
Maximum DCB pressure per balloon, atm†	12.6±2.4 (68)	NA	–
DCB balloon diameter, mm†	3.1±0.4 (25)	NA	–
Post-dilation†	36.0 (9/25)	10.0 (3/30)	0.026
Overall balloon diameter (all balloons used), mm†	3.0±0.3 (25)	2.9±0.4 (30)	0.187
Provisional stent†	8.0 (2/25)	3.3 (1/30)	0.586
Dissections‡			0.108
0	45.8 (11/24)	72.4 (21/29)	
A	0.0 (0/24)	0.0 (0/29)	
B	45.8 (11/24)	24.1 (7/29)	
C	4.2 (1/24)	3.4 (1/29)	
D	4.2 (1/24)	0.0 (0/29)	
E–F	0.0 (0/24)	0.0 (0/29)	
MLD, mm‡	1.945±0.412 (24)	1.797±0.462 (29)	0.230
Diameter stenosis, %‡	31.843±10.959 (24)	34.124±14.368 (29)	0.703
Final residual stenosis, %†	5.1±7.6 (25)	6.8±8.5 (30)	0.432
Device success†,¶	94.1 (64/68)	NA	–
Clinical success‡,#	52.2 (12/23)	40.7 (11/27)	0.570

Values are mean±SD (N) or % (n/N).

* The study sites and core laboratory identified different numbers of target lesions in each treatment group. Study sites identified 25 target lesions in the DCB group and 30 in the PTA group. Therefore, all site-reported lesion characteristics use 25 as the denominator for the DCB group and 30 as the denominator for the PTA group. The core laboratory identified 24 target

lesions in the DCB group and 29 in the PTA group. Therefore, all core laboratory-reported lesion characteristics use 24 as the denominator for the DCB group and 29 as the denominator for the PTA group.

† Site reported.

‡ Core laboratory reported.

§ Significant inflow lesions in the ipsilateral iliac, superficial femoral artery and popliteal arteries needed to be treated successfully prior to enrolment in the study. No other non-target lesions (including outflow lesions) in the target limb were allowed to be treated.

¶ Device success is defined as successful drug delivery, balloon inflation, deflation and retrieval of the intact study device without burst below the rated burst pressure (balloon-based assessment, DCB group only).

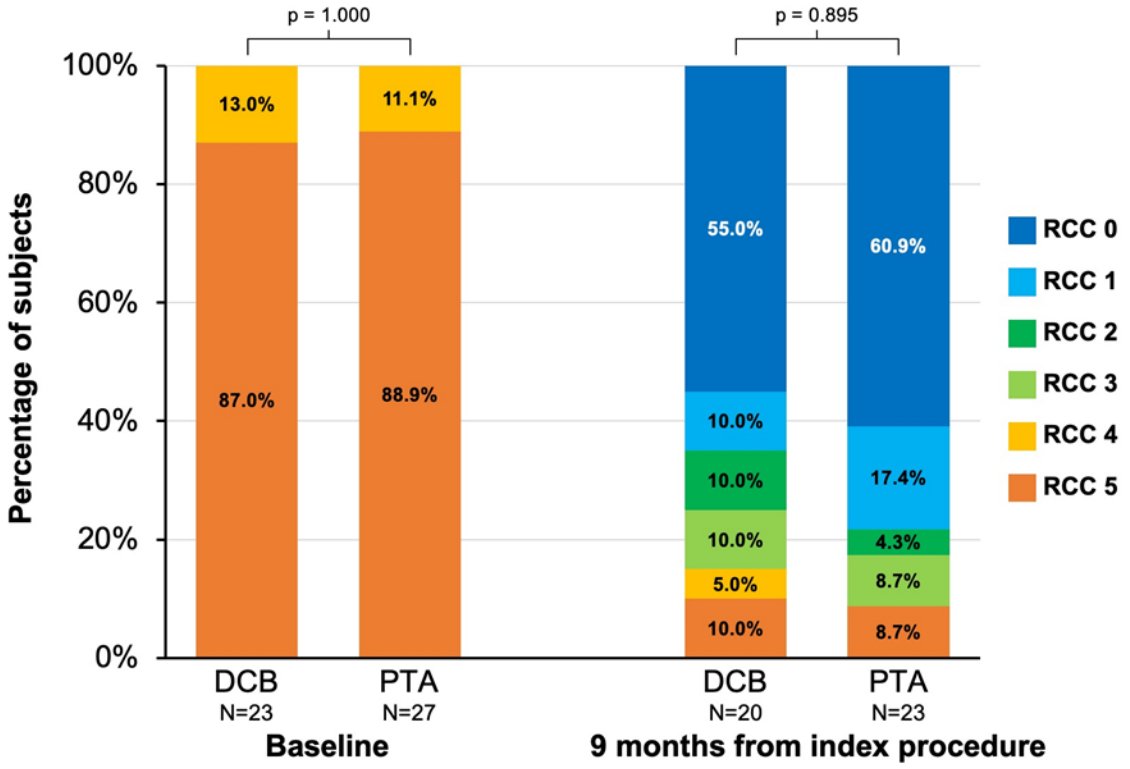
Clinical success is defined as residual stenosis ≤30% without procedural complication (death, major target limb amputation, thrombosis of target lesion, or target vessel revascularisation) prior to discharge (participant-based assessment).

DCB: drug-coated balloon; MLD: minimal lumen diameter; PTA: percutaneous transluminal angioplasty

Supplementary Table 3. Functional flow assessment by duplex ultrasound up to nine months from the IN.PACT BTK randomised study.

	DCB (N=24 lesions*)	PTA (N=29 lesions*)	Difference [95% CI]	*p*-value
Lesions with functional flow at 3 months, %†	93.8 (15/16)	66.7 (14/21)	27.1 [-0.3, 49.0]	0.104
Lesions with functional flow at 6 months, %†	88.2 (15/17)	72.2 (13/18)	16.0 [-11.2, 40.6]	0.402
Lesions with functional flow at 9 months, %†	84.6 (11/13)	60.0 (6/10)	24.6 [-10.9, 55.4]	0.341

Values are % (n/N) unless otherwise indicated.
* Core laboratory analysis determined a total of 24 target lesions in the DCB group and 29 target lesions in the PTA group. All core laboratory-based assessments use these values for counts and proportions.
† Functional flow defined as the absence of target lesion occlusion (no flow) as assessed by duplex ultrasound.
CI: confidence interval; DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty



Supplementary Figure 1. Rutherford clinical category at baseline and month 9 in the IN.PACT BTK randomised study.

Participants in both groups showed clinical improvement in RCC from baseline to nine months after the index procedure. The distribution of participants among RCC categories was not significantly different between groups at baseline (p=1.000) or nine months (p=0.895).

DCB: drug-coated balloon; PTA: percutaneous transluminal angioplasty; RCC: Rutherford clinical category